

APPENDIX A

Research Plan

Title of CRADA

NCI Principal Investigator(s)

Collaborator Principal Investigator(s)

Term of CRADA

Four (4) years

A Letter of Intent (LOI) for this CRADA was executed by and between the Parties on _____.

1. *Research Goals of CRADA*

The overall goal of this research project is to establish the safety and efficacy of Agent in patients, and to provide adequate data to support the registration of Agent in the United States as rapidly as possible.

The goal of phase I of this program will be to establish the safety of Agent, identify the Maximum Tolerated Dose (MTD) and evaluate the pharmacokinetic profile of Agent, in patients with specific malignancies described under Section 3(B) of this Appendix A to the CRADA. The goal of the second phase of this program will be to design and execute clinical trials of Agent that will definitively demonstrate its safety, and its efficacy, in patients with different tumor types.

The Division of Cancer Treatment and Diagnosis (DCTD) and Collaborator shall work together toward the successful development of Agent as a safe and effective novel pharmaceutical compound. The DCTD will provide expertise in designing, implementing and monitoring Phase I and Phase II clinical trials through its intramural and extramural clinical trials network. Additionally, the DCTD will work closely with Collaborator to obtain all the necessary regulatory approval by the U.S. Food and Drug Administration (FDA). Collaborator will provide expertise in the development, formulation and production of Agent. Additionally, Collaborator will work with the DCTD in the design, implementation and monitoring of the clinical trials planned under this CRADA as well as all regulatory aspects and the New Drug Application (NDA) or Biologics License Application (BLA) filings necessary for marketing approval.

[Additional Research Goals may be added if the CRADA is to include preclinical collaborative aspects.]

2. *Background*

A. Scientific (to be provided by Collaborator)

1. Manufacturing, Development and Formulation

- a. Synthetic Process Development
- b. Formulation Development
- c. Preclinical Studies, including the following:

- Acute Toxicity
- Repeat Dose Toxicity
- Efficacy
- Teratology

B. Collaborator organizational or background information (to be provided by Collaborator)

3. *Detailed Description of the Research Plan*

A. Steering Committee

The Division of Cancer Treatment and Diagnosis (DCTD) has utilized the joint Steering Committee concept for the clinical trials CRADAs which are currently active. This has been an extremely useful and efficient method to pursue the collaborative clinical development of an investigational anticancer agent. This committee is comprised of representatives from both the DCTD and the collaborating drug company. Primarily this includes individuals from the clinical and regulatory areas. However, other staff from the toxicology, pharmacology and pharmaceutical development areas are participating members as well, when items pertaining to their area of expertise are discussed.

The CRADA Steering Committee discusses and resolves issues related to:

- Supply of bulk agent;
- Processing and formulation of agent;
- Additional preclinical studies to develop the most advantageous route and schedule, and the best combinations with existing cytotoxic agents;
- The most appropriate clinical studies, including the development of clinical studies to determine the best dose and route of the agent in a tumor where the agent is known to have activity, to provide an efficacious agent to the patient with cost and ease of administration in mind.

The decisions made by the Steering Committee are consensus decisions and include good discussion by all parties in presenting and evaluating the data. The ultimate goal in all the decisions is to ensure that the full potential of the agent is realized with the least cost in terms of the numbers of patients and other resources.

B. Ongoing Phase I Studies

C. Future Clinical Trials (Phase I, II, III)

D. Other Possible Formulations

*[Additional Research Plan Details may include early development preclinical collaborative aspects, as appropriate, depending upon the developmental stage of agent. These additional studies will be mutually agreed upon by NCI and Collaborator prior to initiation of the CRADA. The **Respective Contributions of the Parties**, below, will also be adjusted to reflect these studies.]*

4. *Respective Contributions of the Parties*

A. Joint Responsibilities

1. Representatives of the DCTD and Collaborator will form a Steering Committee, which will be responsible for the design, implementation, oversight and evaluation of the clinical trials.
2. The Steering Committee will evaluate the safety and efficacy of Agent in the initial Phase I and Phase II studies.

This evaluation may include:

- Whether the dose and/or schedule should be modified in order to determine the optimal dose and schedule;
 - Whether other tumor types should be studied;
 - Whether patients with certain organ function limitations should be excluded from the studies as the full toxicity pattern for Agent develops.
3. The DCTD and Collaborator will explore the clinical utility of Agent for the specified cancers. As sensitive tumor types are identified, it will be important to develop combinations of Agent and other active anticancer agents and to compare Agent and Agent combinations with standard therapy for these tumor types. Adjuvant studies may be important in diseases where Agent has activity and where there is a high risk of recurrence following initial primary therapy. Although such further trials are currently beyond the scope of the CRADA, they may be added later by mutual, written agreement under an Amendment to this CRADA, if circumstances warrant.
 4. The parties may collaborate on additional research and development for other indications not outlined in this CRADA. The Steering Committee will propose the scope and magnitude of the collaborative research and development for these additional indications. Such additional studies may be added to the CRADA by Amendment after approval by the Steering Committee, Collaborator and the DCTD.
 5. Both Parties shall collaborate in the collection and analysis of data from clinical trials.
 6. Both Parties will work closely together to ensure that the CRADA clinical trials move forward expeditiously.
 7. Both Parties shall report regularly to the Steering Committee on the progress of the various preclinical and clinical research and development efforts covered by this CRADA.
 8. Subject to the obligations of the Parties to maintain the data generated under this CRADA as confidential and proprietary, the Parties may publicly disclose the results of their research under the circumstances set forth in Article 8.7 of this CRADA, as modified in Appendix C.

9. If the CRADA is terminated, the disposition of data, property, studies and formulated agent will be determined by the Steering Committee in accordance with Article 10 of this CRADA.
10. The Steering Committee will meet within one month of the execution of this CRADA, and then regularly thereafter as appropriate.

B. Collaborator Responsibilities

Collaborator's contribution to the collaborative research and development of Agent includes the following:

1. Usually, Collaborator is responsible for the conduct of the preclinical studies, including such studies as the following:
 - Acute Toxicity
 - Repeat Dose Toxicity
 - Efficacy
 - Teratology

The design of these studies will be mutually agreeable to DCTD and Collaborator representatives.

Preclinical studies will be adequate to meet the FDA requirements for conducting clinical studies and will provide sufficient rationale for the clinical development plan.

Collaborator will be free to sponsor preclinical research and additional clinical research outside the scope of this CRADA.

Collaborator will initiate any new preclinical studies it determines to be necessary for submitting an NDA or BLA. The DCTD may participate in these studies with the mutual agreement and written consent of the DCTD and Collaborator under an Amendment to this CRADA.

2. Collaborator, at its own expense, will supply formulated Agent for all clinical trials set forth in this CRADA. This includes:
 - Supply of Agent for any additional preclinical and clinical studies, approved by both Collaborator and the DCTD, that Collaborator and/or the DCTD may elect to conduct;
 - Supply of Agent for compassionate use, under the circumstances set forth in this CRADA, as determined by the Steering Committee;
 - Supply of Agent for, and any resources necessary for the management of, Group C distribution. Group C distribution shall be initiated if and when the Steering Committee recommends, and the DCTD and Collaborator mutually agree that such action is justified by clinical results and feasible based on adequate agent supply, such that Collaborator's NDA or PLA efforts are not

negatively impacted.

- Collaborator agrees to permit DCTD to supply Agent, or to provide unformulated analytical grade Agent or metabolites, if available, to DCTD extramural investigators for the development of analytical assays or ancillary correlative studies conducted in conjunction with DCTD-approved protocols.

If Collaborator is not in a position to supply Agent, appropriate amendments to the will reflect this.

3. Collaborator will provide resources for data collection and management, beyond that normally carried out by the DCTD, if Collaborator desires such data collection and management, as set forth in the CRADA. This would include the collection of the data required to submit an NDA or BLA to the FDA.
4. Collaborator may provide funds under the CRADA mechanism for partial support of the DCTD-sponsored clinical trials and IND as set forth in CRADA Appendix B.
5. Collaborator will provide funds for travel by DCTD staff to attend meetings concerning Agent clinical trials, as well as funds to supplement DCTD clinical trials (including contracts) as set forth in CRADA Appendix B.
6. Collaborator will prepare and submit an NDA or BLA to the FDA expeditiously when justified by clinical studies, with the object of obtaining pharmaceutical regulatory approval for the commercial marketing of Agent.
7. For activities conducted pursuant to this CRADA in the United States of America, Collaborator agrees to comply with all appropriate DHHS regulations relating to Human Subjects Use, all U.S. Department of Agriculture regulations, and all Public Health Service policies relating to the use and care of laboratory animals. For activities conducted pursuant to this CRADA outside of the United States of America, Collaborator shall conduct such in accordance with GLPs and all applicable rules, regulations and statutes, both local and national, governing such activity in that country.
8. Collaborator agrees to provide to the NCI a redacted version of this CRADA for release under Freedom of Information Act (FOIA) requests.
9. When a CRADA clinical protocol involves either an agent which is proprietary to another pharmaceutical company or involves another NCI collaborative effort, the NCI, the Collaborator and all other collaborators will jointly determine a reasonable and appropriate mechanism for intellectual property and data access and sharing prior to initiation of the clinical trial.

C. DCTD Responsibilities

The Division of Cancer Treatment and Diagnosis (DCTD), NCI contribution to the collaborative research and development of Agent includes the following:

1. The DCTD, as sponsor, has submitted (or will prepare and submit) to the FDA an

Investigational New Drug Application (IND) for Agent.

2. The DCTD will collaborate solely with Collaborator for Agent development, and will assist Collaborator in all aspects of the regulatory approval process.
3. The DCTD will maintain the IND, including all supporting preclinical toxicology data, protocols, investigator qualifications, and other supporting information relative to Agent in DCTD's possession and control, as proprietary and confidential, and make it available exclusively to Collaborator. The DCTD will permit Collaborator to review, cross-reference, and use the IND in conducting clinical trials and in fulfilling all of the requirements necessary for obtaining FDA approval to market Agent.
4. The DCTD will maintain the raw data from all new studies developed under this CRADA in its possession and control, as proprietary and confidential, and make them available exclusively to Collaborator for use in obtaining approval for the commercial marketing of Agent. The DCTD will urge extramural investigators to cooperate exclusively with Collaborator in providing raw data for use in obtaining regulatory approval.
5. When a CRADA clinical protocol involves either an agent which is proprietary to another pharmaceutical company or involves another NCI collaborative effort, the NCI, the Collaborator and all other collaborators will jointly determine a reasonable and appropriate mechanism for intellectual property and data access and sharing prior to initiation of the clinical trial.
6. The DCTD will solicit Letters of Intent (LOI) from the investigators in the DCTD's existing intramural and extramural clinical trials network.

The Protocol Review Committee (PRC), of the DCTD, will:

- Evaluate the rationale of each LOI received at the DCTD;
- Review the LOIs for study design, including dose, schedule and comparison groups, if relevant, in order to address any pertinent scientific questions;
- Examine the characteristics of the patient population to be studied;
- Assess the feasibility of the projected accrual, including the ability of each investigator to accrue the appropriate patient population in a timely manner;
- Review competing studies of the investigator in the specified disease(s);
- Provide investigator(s) with consensus review(s) of the PRC's evaluation to be used to revise the protocol;
- Provide a copy of the consensus review to Collaborator.

The protocols received from investigators in response to the approved LOIs will be reviewed and evaluated by the PRC. The PRC will:

- Evaluate each protocol from the agent, disease, statistical and regulatory perspectives in order to ensure that the study design that was approved by the PRC at the LOI stage is carried out;
- Provide Collaborator with copies of the protocols to enable Collaborator the opportunity to raise any issues they feel are pertinent to the studies. Comments from Collaborator received by CTEP before the Protocol Review Committee meeting will be discussed by CTEP and incorporated in the protocol, absent good cause. The revised protocols will be evaluated again by each of the CTEP reviewers to ensure the points raised have been addressed.

In addition, the PRC will review any correlative laboratory studies, solicited from investigators, to address cellular pharmacological and/or pharmacokinetics questions as necessary. These studies will be proposed by the Steering Committee and will be approved by both the DCTD and Collaborator.

7. The DCTD will evaluate each of the active studies as they progress to ensure that the appropriate questions are being addressed and to ensure that the studies are modified as required based on the developing data. The DCTD will utilize its existing procedures and mechanisms to follow the clinical studies to ensure that all studies meet the pertinent FDA regulations.

5. *List of Scientific References (Optional)*

6. *Abstract of the Research Plan for Public Release*

This abstract of the CRADA Research Plan, or a similar abstract approved by the DCTD and Collaborator, may be released to the public:

The National Cancer Institute and Collaborator will collaborate in the conduct of clinical trials of Agent. This Agent has shown promising activity in [cancer(s)]. The National Cancer Institute and Collaborator will collaborate in the clinical development of Agent to provide the best treatment options to patients with specific cancer indications and to ultimately obtain approval of Agent as a commercial anticancer agent.